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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,358	08/11/2006	Austin Gerard Smith	09641.0011-00000	1585

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,358	SMITH ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/9/09, 1/11/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8-16 and 28-30* is/are pending in the application.

4a) Of the above claim(s) *30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-16,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 1/11/10 to claims 1, 12, 15, and 28 have been entered. Claims 3, 17-27, and 31-38 have been canceled in this reply. No claims have been added. Claims 1, 2, 4-6, 8-16, and 28-30 remain pending in the current application, of which claims 1, 2, 4-6, 8-16, 28, and 29 are being considered on their merits. Claim 30 remains withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

The 1/11/10 claim listing does not reflect claim 30's proper status, i.e. withdrawn. See page 2 of 6/12/09 Office action. Future claim listings that do not indicate claims' proper status will be held nonresponsive.

Election/Restrictions

Applicant's election of the species "genetically altered to include exogenous DNA" and "LIF" in the reply received 3/27/09 is still in effect over the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 and 16 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 requires culturing the cell in medium containing an Id protein and then activating gp130 downstream signaling, but the scope of this step is not clear because it is defined wholly using functional language. While describing an element in terms of its function is not itself improper (see *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)), claims directed to a product should be distinguished from the prior art product in terms of structure rather than function; this point was recently revisited. "When a claim limitation is defined in purely functional terms, the task of determining whether that limitation is sufficiently definite is a difficult one that is highly dependent on context (e.g., the disclosure in the specification and the knowledge of a person of ordinary skill in the relevant art area). We note that the patent drafter is in the best position to resolve the ambiguity in the patent claims, and it is highly desirable that patent examiners demand that applicants do so in appropriate circumstances so that the patent can be amended during prosecution rather than attempting to resolve the ambiguity in litigation." *Halliburton Energy Services, Inc. v. M-I LLC*, 85 USPQ2d 1654, 1663 (Fed. Cir. 2008). Such ambiguity could be resolved in a few ways, for example by providing a quantitative metric for the property, or a formula for calculating the claimed functional property along with examples and counterexamples of products with that property. While functional claiming is authorized by 35 U.S.C. § 112, sixth paragraph, that statute was enacted specifically to preclude overly broad claims that effectively purport to cover any and all limitations, so long as they perform the required functions. Specifically, claims that are ambiguous as to boundaries for functional limitations may be indefinite and do not distinguish the claimed product over the prior art.

Because claims 13, 14, and 16 depend from indefinite claim 12 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph. The examiner suggests that applicant consider incorporating the limitations of claim 15 into claim 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-6, 8-16, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noguiera et al. (2000, *Biochemical and Biophysical Research Communications* 276: 803-812; on IDS) taken in view of Benezra et al. (1990, *Cell* 61: 49-59), Smith et al. (1999, U.S. Patent 5,871,961), Blackburn et al. (2002, U.S. Patent Application Publication 2002/0146689), and Carpenter et al. (2001, WO 01/51616; reference N).

Noguiera teaches culturing mouse embryonic stem (ES) cells in medium supplemented with LIF (page 804, column 1, under "ES cell culture). Noguiera teaches that cells so cultured remain undifferentiated (page 804, column 2, under "ES cell differentiation").

Noguiera does not teach culturing ES cells with an Id gene product, e.g. an Id protein. Noguiera does not teach expressing an Id gene product, e.g. an Id protein, in

ES cells. Noguiera does not teach culturing ES cells in serum-free, feeder-free medium.

Benezra teaches a cDNA that encodes the inhibitor of differentiation (Id) gene and its product, a helix-loop-helix (HLH) protein (page 50, column 1; and Figure 1). Benezra teaches that Id is downregulated upon differentiation (page 50, column 2) and that transfecting undifferentiated cells with Id cDNA inhibits their differentiation (pages 53-54). Benezra suggests expressing Id in additional cell types (page 54, column 1).

Smith teaches methods for producing recombinant histidine-tagged CR8 (his_6-CR8), a HLH protein, in an *E. coli* expression system and methods for purifying his_6-CR8 on a nickel column (column 73, line 63, through column 74, line 27). Smith teaches that his_6-CR8 protein so produced and isolated retains its ability to bind DNA (column 78, lines 32-56).

Blackburn teaches vectors and methods for expressing cDNAs of interest episomally in ES cells (Example 1 at paragraphs 98-126, as well as paragraphs 19, 59-61, and 80). Blackburn's method results in extremely high rates of transfection (paragraph 121) and varying levels of expression (paragraph 124-126).

Carpenter teaches culturing human ES cells in the absence of feeder cells (page 13, line 36, through page 14, line 16). Carpenter's culturing step is carried out with feeder cell-conditioned medium (CM; page 17, line 37, through page 19, line 38). The medium administered to feeder cells for making CM may be serum-free (page 18, lines 10-15). ES cells cultured in the method of Carpenter remain undifferentiated (Table 1 at

page 38). ES cells cultured in the method of Carpenter are suitable for transfection with exogenous DNA (page 48, line 34, through page 50, line 35).

A person of ordinary skill in the art would have had a reasonable expectation of success in preparing recombinant Id protein by cloning the Id cDNA taught by Benezra into the expression vector taught by Smith and recovering purified, active his_6-Id using the method of Smith because both Id and CR8 are HLH proteins; the skilled artisan would have had a further reasonable expectation of culturing ES cells in media containing purified his_6-Id because Smith teaches that purified HLH proteins retain biological activity and are, therefore, suitable for biological systems. The skilled artisan would have been motivated to include purified, active his_6-Id in the medium of Noguiera because Benezra teaches that Id inhibits differentiation, and Noguiera's medium contains LIF, which also inhibits differentiation. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06.

The skilled artisan would have had a further reasonable expectation of success in expressing the Id cDNA of Benezra using the system and method of Blackburn in the ES cells of Noguiera because Blackburn and Carpenter teach that any cDNA may be expressed in ES cells. The skilled artisan would have been motivated to express Id in the ES cells of Noguiera in order to maintain the ES cells in an undifferentiated state

until differentiation is desired; given the teachings of Benezra, the skilled artisan would have had a reasonable expectation that transfecting ES cells with Id would inhibit their differentiation.

The skilled artisan would have had a further reasonable expectation of success in substituting the serum-free, feeder-free conditions of Carpenter for the serum-containing medium of Noguiera because both sets of conditions may be used to maintain ES cells in an undifferentiated state and are, therefore, functional equivalents for each other. Substituting one for the other would have been obvious at the time of the invention. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce and to purify Id protein as directed by Smith and Benezra and to include such protein in the culturing of Noguiera because combining Id and LIF in a single medium would be expected to maintain the ES cells of Noguiera in an undifferentiated state. It would have been further obvious to transfect the ES cells of Noguiera with the Id cDNA of Benezra using the expression system and method of Blackburn in order to keep the ES cells in an undifferentiated state by combining the known effects of Id and LIF on ES cell proliferation. It would have been further obvious to culture the ES cells of Noguiera in serum-free, feeder-free conditions

as directed by Carpenter containing the LIF of Noguiera and the purified Id suggested by Benezra and Smith in order to keep the ES cells in an undifferentiated state; it would have also been obvious to transfect the ES cells of Noguiera with Id cDNA as taught by Benezra and Blackburn and then to culture the transfected cells in the serum-free medium of Kaufman further containing the LIF of Noguiera for the same reasons. The art establishes that the serum-free, feeder-free conditions of Carpenter, the LIF in the medium of Noguiera, and the Id protein of Benezra in view of Smith and Blackburn all have the same explicitly stated utility of inhibiting differentiation in undifferentiated cells, so combining these three components would have been obvious at the time the invention was made.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the art does not teach that Id inhibits differentiation. See 10/9/09 reply, pages 10-11. Applicant alleges that the art does not teach culturing ES cells in serum-free, feeder-free conditions. See 10/9/09 reply, pages 11-12. These arguments have been fully considered, but they are not persuasive.

Benezra teaches that transfecting C3H10T1/2 cells with Id inhibits MyoD-dependent trans-activation of the MCK enhancer; the MCK enhancer drives muscle differentation. See the legend to Figure 6 at page 55; the section bridging pages 53-54; and page 49, last paragraph of the introduction section. Benezra also discusses "the decrease in [Id] expression upon differentiation in erythroid, muscle, and EC cell lines," implying an inverse relationship between Id expression and differentiation. See page

55, last paragraph, continuing to page 56. Benezra teaches that cells downregulate Id when they withdraw from the cell cycle, i.e. differentiate. See page 50, second paragraph of column 2. Furthermore, Nogueira refers to "the generally accepted idea that Id genes are expressed strongly in undifferentiated cells" and teaches that the Id genes' best-characterized function is to inhibit lineage-specific gene expression. See page 809. Noguiera cites numerous references that also characterize Id as an inhibitor of differentiation. See references 2, 5, 6, 15, 22, 23, and 43, e.g. Indeed, Ying et al. (2003, *Cell* 115: 281-292), cited on applicant's IDS, teaches that Id blocks ES cell differentiation and promotes self-renewal. See page 286, last paragraph, continuing to page 287. The cited art indicates that at the time of the invention, skilled artisans associated high levels of Id expression with maintenance of an undifferentiated state in ES cells. The basis for applicant's contentions to the contrary are unclear.

The limitation requiring that the culturing step be carried out in the absence of feeder cells was presented for the first time in this reply. The examiner believes that the newly cited Carpenter reference fully addresses applicant's arguments on this subject.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651